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Brief communication

Subtle cognitive deficits in severe alcohol addicts – Do they show a specific profile?

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Although alcohol dependency is a burden to society, data on cognitive performance in therapy-resistant patients after multiple withdrawals are poor. In this study, 22 patients without reported cognitive deficits and 20 control subjects performed extensive cognitive testing and a motor task assessing short-term memory. Patients displayed subtle deficits (mainly in executive function), while memory functions were relatively unimpaired. Our results suggest that subtle frontal-executive deficits may contribute to a poor prognosis, but could be missed by routine clinical tests.

Alcohol dependency is a major burden on society and a devastating disease for many affected individuals. Despite various therapeutic approaches, a proportion of patients do not respond to therapy and suffer relapses shortly after hospitalized detoxification and/or withdrawal.

While evidence indicates that mild-to-moderate alcohol consumption has neuroprotective effects on cognitive function (Stampfer, Kang, Chen, Cherry, & Grodstein, 2005), excessive drinking has been linked with structural brain damage and deterioration of cognitive performance (Green *et al.*, 2010). The frontal lobes, cerebellum and limbic system appear more vulnerable to the toxic effects of alcohol than other brain areas

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(Oscar-Berman & Marinkovic, 2007). In particular, several animal studies examining recurrent withdrawals have demonstrated frontal lobe damage due to glutamate-related excitotoxicity (De Witte, Pinto, Ansseau, & Verbanck, 2003; Loeber *et al.*, 2010; Stephens & Duka, 2008). Unfortunately, studies investigating the neuropsychological sequelae of multiple withdrawals in humans are scarce and provide inconclusive results (Duka, Townshend, Collier, & Stephens, 2003; Loeber *et al.*, 2009, 2010). Furthermore, no studies have examined severely affected individuals who have experienced at least five relapses. We hypothesized that such therapy-resistant patients would suffer from subtle cognitive deficits, especially in frontal-executive functions.

Materials and Methods

A total of 22 inpatients and 20 healthy control subjects were recruited. All subjects gave informed consent, and the study was approved by the local ethics committee. All patients were diagnosed by a senior psychiatrist as being alcohol-dependent according to the criteria of the International Classification of Diseases (ICD) 10 (F10.2), and were clinically examined by an experienced neurologist. Additional criteria included a history of more than 5 years of drinking, and to have experienced at least five withdrawals in the last 5 years. Testing took place between days 7 and 21 of withdrawal, to examine a homogenous population and to represent the acute phase shortly before discharge. Subjects using diazepam or clomethiazol were not tested until at least 7 days after their final medication. Patients with elevated ammonium levels, hypovitaminosis, hypothyroidism, electrolyte disturbances, or parameters indicating an acute inflammation were excluded. Apart from mild dysthymia, all central nervous system (CNS)-affecting diseases, cognitive complaints and CNS-affecting drugs were further exclusion criteria. Three patients did not undergo all neuropsychological subtests for compliance reasons. The control group was closely matched by age, education, and gender. One control subject was excluded because of a previously undiagnosed major depression, and a further matched pair could not be found.

Neuropsychological test battery

The following well-established cognitive tests were performed by a senior neuropsychologist as described in the literature: Digit Span subtest of the Wechsler Adult Intelligence Scale, Version III (WAIS-III), the two classical versions of the Trail Making Test (TMT-A, TMT-B), Benton facial recognition test, Syndrom-Kurz-Test (SKT), Facially Expressed Emotion Labeling (FEEL), and a German version of the verbal learning memory test (VLMT). The Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B), a multiple-choice vocabulary intelligence test, was used to provide an estimation of crystalline intelligence. The Regensburg Wortflüssigkeitstest (RWT), a word fluency test containing verbal and phonological fluency with alternating categories, was also applied. The Becks Depression Inventory, second version (BDI-II), was completed as a self-questionnaire.

Motor short-term memory paradigm

All participants performed a computerized motor short-term memory paradigm. Subjects were required to memorize a 4-, 5-, or 6-item finger sequence, which was indicated by a dot moving on the fingers of a schematic of the left hand or right hand. A go cue was

presented either immediately or after a 5- to 7-s pause, and the memorized finger sequence had to be reproduced as quickly and accurately as possible. Each sequence length was combined with both types of delay and the two possible hands, yielding 12 distinct conditions. Each condition was presented six times throughout the whole experiment. Thus, in total, 72 trials were presented in a randomized fashion. All visual stimuli were displayed using the presentation software package (Version 12.0). A standardized finger-tapping test was performed to exclude motor dysfunction.

Data analysis

Measurements from the neuropsychological assessment, the motor paradigm and sociodemographic data were analysed offline using MATLAB (Mathworks, Natick, MA). Group differences were analysed using two sample *t*-tests. Correlations were calculated by Spearman's rank. Gender distribution was tested by a chi-square test. Performance in the short-term memory paradigm was assessed using a repeated measures analysis of variance (rmANOVA) with within-subject variables of sequence length (four, five, or six items) and timing (immediate, delayed), and a between-subjects factor of group (patients, controls).

Results

Clinical characteristics

Patients and controls did not significantly differ in terms of gender ($\chi^2 = 0.38, p = .845$), age ($T_{40} = 0.08, p = .94$), or education ($T_{40} = 0.98, p = .33$). Detailed baseline characteristics are shown in Table 1. Patients had a mean daily ethanol intake of 241.8 g (307 mL, ≈31 UK units of alcohol or 15 "beer-units") before actual withdrawal therapy. Patients reported a mean of 8.9 hospitalizations for alcohol withdrawal therapies.

Neuropsychological test battery

Detailed data from the neuropsychological test battery are provided in Table 2. Patients showed significantly lower performance in the subtests TMT-A ($T_{40} = 2.7; p = .01$), TMT-B ($T_{40} = 3.0, p = .004$), and RWT ($T_{39} = 8.1, p < .001$) compared with the control group, indicating a specific frontal-executive deficit. The patient group also displayed lower performance in the Benton Test ($T_{40} = 2.9, p = .006$) and MWT ($T_{39} = 2.6, p = .01$). Additionally, patients reported a significantly greater level of subclinical depressive features in the BDI-II ($T_{37} = 4.3, p < .001$). In contrast, learning, direct, and delayed memory were not impaired in comparison with the control group.

Table 1. Baseline characteristics

	Patients	Controls
Male/female	16/6	15/5
Age	46.8 ± 7.4	46.8 ± 6.5
Mean drink units/day	14.8 ± 1.1	0–1
Mean ethanol intake gram/day	241.8 ± 17	<10
Mean number of hospitalized withdrawal therapies	8.94	0
Years of education	10.0 ± 1.9	11.0 ± 1.85

Table 2. Group differences between patients and controls by two sample *T*-test

	N	*M*	*SD*	*p*	*df*
Mehrfachwahl-Wortschatz-Intelligenztest (vocabulary intelligence testing)					
Patient	21	26.19	4.273	**.012**	39
Control	20	29.40	3.440		
Digit Span subtest of the Wechsler Adult Intelligence Scale (forward)					
Patient	22	7.73	2.028	.967	40
Control	20	7.75	1.482		
Digit Span subtest of the Wechsler Adult Intelligence Scale (backward)					
Patient	22	5.86	2.007	.522	40
Control	20	6.20	1.240		
Verbal Learning and Memory Test 1					
Patient	21	45.33	8.248	.403	39
Control	20	47.45	7.749		
Verbal Learning and Memory Test 2					
Patient	21	9.52	2.994	.546	39
Control	20	8.95	3.034		
Verbal Learning and Memory Test 3					
Patient	21	2.29	1.901	.394	39
Control	20	2.95	2.946		
Trail Making Test Part A					
Patient	22	31.00	7.856	**.010**	40
Control	20	25.00	6.274		
Trail Making Test Part B					
Patient	22	67.09	26.106	**.004**	40
Control	20	46.75	15.151		
Regensburg Wording Test					
Patient	21	53.33	14.524	**.000**	39
Control	20	92.35	16.001		
Benton facial recognition test					
Patient	22	6.50	2.841	**.006**	40
Control	20	4.30	2.793		
Syndrom-Kurz-Test					
Patient	21	3.00	2.408	.117	39
Control	20	1.90	1.944		
Beck Depression Inventory					
Patient	19	16.11	9.820	**.000**	37
Control	20	5.50	4.628		
Facially Expressed Emotion Labeling					
Patient	21	28.29	3.133	.823	38
Control	19	27.89	7.249		

Note. *M*, mean; *SD*, standard deviation; *df*, degree of freedom; significant results on a 0.05 level are indicated in bold.

Motor short-term memory paradigm

A significant main effect of sequence length revealed that participants made fewer errors for shorter sequences ($F_{78} = 156.6$, $p < .001$, four items = 56.9 ± 3.7%, five items = 35.1 ± 3.7%, six items = 15.8 ± 2.4%). A significant main effect of timing revealed that participants made fewer errors when repeating sequences immediately ($F_{39} = 25.1$, $p < .001$, immediate = 40.3 ± 3.2%, delayed = 31.6 ± 3.2%). The rmANO-

Table 3. Correlation between motor short-term memory paradigm and cognitive tests

	Motor paradigm direct recall	Motor paradigm delayed recall
Motor paradigm direct recall ($N = 42$)		
r	1.000	.851
p	–	**.000**
Motor paradigm delayed recall ($N = 42$)		
r	.851	1.000
p	**.000**	–
Wechsler Adult Intelligence Scale (forward, $N = 42$)		
r	.086	.022
p	.586	.888
Wechsler Adult Intelligence Scale (backward, $N = 42$)		
r	.497	.461
p	**.001**	**.002**
Trail Making Test Part A ($N = 42$)		
r	−.045	−.036
p	.780	.823
Trail Making Test Part B ($N = 42$)		
r	−.311	−.274
p	**.045**	**.079**
Regensburg Wording Test ($N = 42$)		
r	.169	.126
p	.291	.434
Verbal Learning and Memory Test (total score, $N = 41$)		
r	.301	.339
p	.056	**.030**
Benton Test (correct rate, $N = 42$)		
r	.533	.470
p	**.000**	**.002**
Syndrom-Kurz-Test ($N = 41$)		
r	−.044	−.194
p	.784	.224
Becks Depression Inventory ($N = 41$)		
r	−.183	.031
p	.265	.851

Note. *r*, Spearman's rank correlation. Significant results on a 0.05 level are indicated in bold.

VA revealed no further significant effects, and critically, no significant differences were revealed between groups (all $p > .50$).

There was a significant correlation between the motor recall abilities of the paradigm and the subtests WAIS-III backward, TMT-B, and Benton which are presented in detail in Table 3. All other group comparisons and correlations were not significant as outlined in Tables 2 and 3.

Discussion

Our main finding was that, as hypothesized, therapy-resistant heavy drinkers without subjective cognitive complaints displayed subtle cognitive deficits compared with the control group. The cognitive impairments primarily affected frontal-executive functions,

while memory was relatively spared. The latter was true for both classical verbal tests and the computerized motor short-term memory paradigm. The finding that patients did not differ from controls in either of these tests argues against a differential impairment of verbal versus action-related memory functions. Performance on the short-term memory motor task was correlated with the Benton Test, TMT-B, and WAIS-III backwards, indicating that it provided a combined assessment of memory and visuospatial functions.

The finding that patients displayed frontal-executive deficits is consistent with animal studies that demonstrate frontal lobe damage arising through glutamate-mediated excitotoxicity due to recurrent detoxifications (De Witte *et al.*, 2003). Frontal-executive functions are known to include the ability to plan ahead and to overcome impulsive behaviour. It would therefore follow that frontal-executive impairments would correlate with the occurrence of relapses. Unfortunately, no studies to date have provided convincing data to support this proposal (Bowden, Crews, Bates, Fals-Stewart, & Ambrose, 2001). A recent study by Loeber *et al.* (2010) demonstrated a negative effect on cognitive function and recovery in 31 patients. However, they did not show a correlation with the occurrence of relapses, and included participants with a relatively positive prognosis. In contrast, the study presented here examined only patients with a history of being resistant to therapy, who can therefore be assumed to have a negative prognosis. Our study thus provides preliminary support for a negative association between frontal-executive deficits and future prognosis, although further longitudinal data and replication with larger cohorts are required.

A clinical implication may be drawn from these results based on data indicating that cognitive deficits tend to improve with abstinence (Fals-Stewart & Lam, 2010). It may hence be assumed that patients with subtle executive deficits may benefit most from long-term therapeutic options rather than from frequent detoxifications. It is also noteworthy that the cognitive deficits manifested solely in more dedicated neuropsychological tests (TMT and RWT), and would therefore probably have been missed by routine clinical tests. Similarly, while patients did not fulfil the ICD10 criteria for depressive syndrome, they reported significantly more depressive features in the BDI questionnaire compared with controls. These depressive tendencies may have aggravated executive impairments, but also would not have been detected in routine clinical tests.

In summary, the study presented here found that severely alcohol-dependent subjects who have experienced recurrent withdrawals display subtle cognitive deficits. These deficits occurred primarily in the frontal-executive domain, while memory functions and visuospatial capacities were largely spared. Our pilot study therefore suggests that extensive cognitive testing might be a helpful additional tool in assessing therapy-resistant heavy drinkers. Future trials will elucidate the influence these cognitive deficits have on prognosis and quality of life.

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